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Original Research

Is the presence of tumor cavitation important in stage III lung squamose cell cancer?

Effect of tumor cavitation on prognosis

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Abstract
Aim: Tumor cavitation is seen most frequently in the lung squamous cell cancer subtype (SCC). We aimed to evaluate the prognostic significance of tumor cavitation at the time of diagnosis and survival in patients with lung SCC.
Material and Methods: Stage I-IV lung SCC patients aged >18 years between 2016-2021 were retrospectively analyzed. The presence of tumor cavitation in the patients and its effect on clinical and prognosis were evaluated. The effects of inflammatory indexes on prognosis were investigated. Progression-Free Survival (PFS) and Overall Survival (OS) times were examined.
Results: Thirty-eight patients with tumor cavitation and 66 without tumor cavitation were examined. The frequency of tumor cavitation in lung SCC was 16.8%. Most of the patients with tumor cavitation consisted of men with large tumor diameter, heavy smokers, and advanced stage. The monocyte- lymphocyte ratio and lactate dehydrogenase levels were lower in those with tumor cavitation (p=0.002, p=0.010). Tumor cavitation significantly reduced OS in Stage III lung SCC (17.83 vs 40.53 months, p=0.016). However, the presence of tumor cavitation did not affect PFS or OS in the whole population (p=0.759, p=0.256). High neutrophil-lymphocyte ratio and advanced stage were independent factors affecting OS (p=0.048, p=0.009).
Discussion: Tumor cavitation is a clinical entity that differs in its biology and clinical course. It is a poor prognostic factor in Stage III lung SCC patients.

Keywords
Tumor Cavitation, Squamous Cell Lung Carcinoma, Inflammatory Score, Prognosis, Survival

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Introduction

Squamous cell cancer (SCC) is the most common type of non-small cell lung cancer after adenocarcinoma. Lung SCCs consist of heterogeneous tumors with different biological characteristics and clinical behavior [1,2]. The scarcity of targeting mutations, their histopathological and genetic features and difficulties of diagnosis, cause the prognosis of this patient group to be worse.

Cavitation can be seen in 10-22% of lung cancers [3,4]. Tumor cavitation is thought to be caused by rapid tumor growth and, as a result, insufficient blood flow to the central lesion, ischemia, infection, or the drainage of necrotic material from the bronchi, which occurs with central necrosis [3,5]. Tumor cavitations are large, high-grade, peripherally located tumors that are most commonly seen in lung SCCs [6]. Tumor cavitation causes delay in the diagnosis of cancer in patients, and difficulties in treatment in patients with diagnosis due to complications that develop in the patient.

In the literature, there are conflicting results between tumor cavitation in lung cancer patients and tumor control and survival. We aimed to evaluate the effect of tumor cavitation on prognosis, its relationship with inflammatory indexes, and its effect on Overall Survival (OS) in patients with lung SCCs at the time of diagnosis.

Material and Methods

Squamous cell lung cancers who applied to the Medical Oncology outpatient clinics of two centers between 2016 and 2021 were evaluated retrospectively.

Ethics Statement:

The study protocol was approved by the local ethics committee of the study center (Approval Date: 29.12.2021 No: 2021-24/10).

Inclusion criteria were as follows:

1. Patients over 18 years of age
2. Oncologic treatment applied for lung SCCs
3. Follow-up at least six months
4. Finding hemogram and biochemistry values at the time of diagnosis
5. Evaluation of staging at diagnosis with thorax computered tomography, a fluorodeoxyglucose (FDG)-positron emission tomography (PET CT) and brain magnetic resonance scan.

Exclusion criteria were as follows:

1. The presence of a synchronous or metachronous tumor
2. Using vascular endothelial growth factor treatment
3. The presence of immunosuppresive disease
4. The presence of brain metastasis at diagnosis.

Clinical, demographic, tumor characteristics, primary tumor PET CT the maximum standardized uptake value (SUVmax) level and presence of tumor cavitation in the patients were evaluated. American Joint Committee on Cancer 8th Edition was used for T (tumor), N (lymph node) and M (metastasis) classification in clinical and pathological staging [7]. Primary tumor PET CT Eastern Cooperative Oncology Group (ECOG) level was calculated by taking the highest cavitary-noncavitary metabolic value in the primary tumor. Oncological treatments (surgery, chemotherapy, radiotherapy, immunotherapy) applied for lung SCC were examined.

Assessment of tumor cavitation:

Tumor cavitation was evaluated by a five-year radiologist specialist as an abnormal space in the lung parenchyma containing fluid or air by examining the thorax computered tomography images.

Evaluation of inflammatory markers:

Hemogram and biochemistry analyses at the time of diagnosis were evaluated with xn1000 Sysmex and Cobas-e 801 analytical unit in one center, and with Sysmex xn2000 and Beckman coulter Au5800 in the other center.

Neutrophil lymphocyte ratio (NLR), platelet lymphocyte ratio (PLR), monocyte lymphocyte ratio (MLR), SII-score (SII=Neutrophil×Platelet/Lymphocyte), Hemoglobin Albumin Lymphocyte and Platelet (HALP)-score [hemoglobin(g/L)×albumin(g/L)×lymphocytes(/L)/platelets(/L)] and anemia were examined [8-12]. The presence of anemia was evaluated as <12g/dL in the population consisting of mostly male patients receiving oncological treatment. Receiver Operating Characteristic (ROC) analysis was performed to determine the threshold level of inflamatuar indexes. The threshold values for NLR; 2.1859, PLR; 130.56, MLR; 0.4125, SII-score; 604.65 and HALP-score; 29.1545 were used, respectively.

Survival analyses:

Progression-Free Survival (PFS) was calculated as the time of diagnosis to first progression, and OS was calculated as the time of diagnosis to death or last follow-up.

Statistic:

After the obtained data were coded, they were analyzed using the SPSS program version 22.0. Descriptive statistics of evaluation results: numbers and percentages for categorical variables, median and interquartile range (IQR) for numerical variables. Comparisons of numerical variables between two independent groups; Since the normal distribution condition was not met, it was evaluated with the Mann-Whitney U test. The Chi-square test was used to compare qualitative data. The Kaplan-Meier test was used for survival analysis. Univariate and multivariate Cox-regression analysis was performed to determine Hazard ratios (HRs) and 95% Confidence intervals (CIs). Factors that were determined to be significant only according to the univariate analyzes were then included in the multivariate analyses. Statistical alpha significance level was accepted as $p<0.05$.

Results

A total of 88 lung SCCs were screened in one of the centers and the data of 40 patients were evaluated within the scope of the study. In the other center, 137 patients with lung SCC were screened and 64 of these patients were included in the study. When patients of the two centers were evaluated, it was seen that 225 (33.9%) of 663 lung cancer patients had lung SCC and TC was observed in 38 (16.8%) patients. In the study, the data of 38 patients with tumor cavitation and 66 patients without tumor cavitation were evaluated.

Ninety (86.5%) patients were male, the mean age was 60.34 ±8.0 (33-76) years. Age, gender, the maximum standardized uptake value (SUVmax) performance status, smoking, comorbidity, TNM stage and primary tumor localization between patients with and without tumor cavitation are shown in Table 1.

There was no significant difference in demographic and clinical characteristics between patients with and without tumor cavitation at diagnosis.

The FDG-PET CT SUVmax level of the primary tumor was 10.17±5.38 (4-31.6). FDG-PET CT SUVmax level did not differ with the presence of tumor cavitation (p=0.316). The mean hemoglobin level in the patients was 11.258±1.73 g/dL (8.8-16.5). When the inflammatory indices between those with and without tumor cavitation were examined, it was observed that MLR and lactate dehydrogenase (LHD) levels were lower in those with tumor cavitation (p=0.002, p=0.010). It was observed that LDH level increased as the stage increased [194 U/L (173-242.5) in Stage I,II; 205 U/L (162.5-323) in Stage III and 375 U/L (192.5-598) in Stage IV, p=0.001].

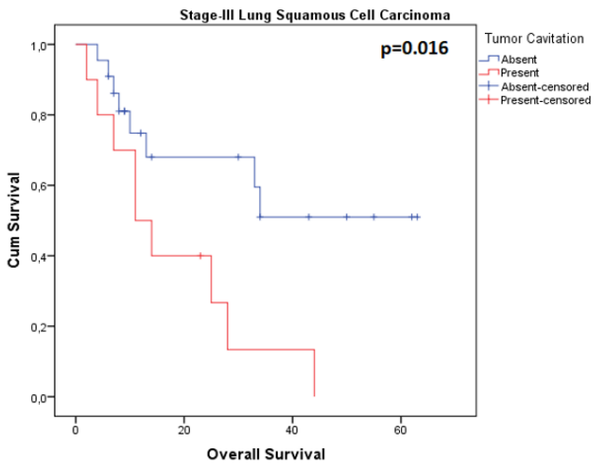

Figure 1. Comparison of overall survival in patients with tumor cavitation absent and present patients in Stage III lung squamous cell carcinoma.

Twenty-four (23.1%) patients underwent lung surgery. In terms of oncological treatments, six patients (5.8%) underwent surgery only, 20 (19.2%) underwent neoadjuvant/adjuvant chemotherapy±radiotherpy, 24 (23.1%) underwent definitive chemoradiotherapy/radiotherapy, 49 (47.1%) underwent palliative chemotherapy, and five (4.8%) underwent immunotherapy± chemotherapy. 96 (92.3%) patients received chemotherapy.

Local recurrence was observed in 23 (22.1%) patients and distant metastases developed in 55 (52.9%) patients. Second progression was observed in 45 (43.3%) patients. Relapse/metastasis was more common in patients with anemia at diagnosis (p=0.009). In addition, patients with recurrence/metastasis had higher diagnostic LDH levels (p=0.001). The median PFS was calculated as eight months (4.5-11.5) in lung SCCs 13 months (10.5-15.5) in patients with tumor cavitation, and seven months (5.3-8.7) in non-tumor cavitation patients (p=0.759). While chemotherapy was given to 79.4% (62 patients) of the patients who developed recurrence/metastasis, radiotherapy was applied to 12 (15.3%) patients,

Table 1. Demographic, clinical and tumor characteristics of patients

	Total (%) n= (104)	Tumor Cavitation Present (%) n= 38 (36.5)	Tumor Cavitation Absent (%) n=66 (63.5)	p
Age (mean or median)	62 (54.25-67.0)	61.5 (53.8-68)	62 (55.8-65)	0.779 *
Gender				
Female	14 (13.5)	5 (13.2)	9 (13.6)	1.000 †
Male	90 (86.5)	33 (86.8)	57 (86.4)	
Smoking Status				
Present	92 (88.5)	34 (89.5)	58 (87.9)	1.000‡
Absent	12 (11.5)	4 (10.5)	8 (12.1)	
ECOG Performance Status**				
ECOG PS 0-1	71 (68.2)	25 (65.8)	46 (69.7)	0.847 †
ECOG PS 2-3	33 (31.7)	13 (34.2)	20 (30.3)	
Comorbidities, n(%)				
Yes	90 (76.9)	27 (71.1)	53 (80.3)	0.403 †
No	24 (23.1)	11 (28.9)	13 (19.7)	
Tumor size, cm	6.2 (5-7.7)	6 (5-7.4)	6.4 (5-8.4)	0.410*
Primer Tumor Suv Max, Before Treatment, median (IQR)	8.6 (6.7-12.7)	9.6 (6.9-12.6)	8 (6.2-13.1)	0.316*
Primer Tumor Lung Localisation				
Left Lung	60 (57.7)	16 (42.1)	28 (42.4)	1.000 †
Right Lung	44 (42.3)	22 (57.9)	38 (57.6)	
Primer Tumor Lung placement				
Central	39 (37.5)	15 (39.5)	24 (36.4)	0.916†
Peripheral	65 (62.5)	23 (60.5)	42 (63.6)	
Clinical Stage, n (%)				
Stage I -II	20 (19.2)	8 (21.1)	12 (18.2)	0.751†
Stage III	32 (30.8)	10 (26.3)	22 (33.3)	
Stage IV	52 (50.0)	20 (52.6)	32 (48.5)	
Progression Free Survival (PFS) (month)	8 (4.5-11.5)	13 (10.5-15.5)	7 (5.3-8.7)	0.759§
Overall Survival (OS) (month)	22 (17.3-26.7)	21 (11.2-30.8)	23 (13.4-32.6)	0.256§

*Mann-Whitney U test, †Chi-Square Test, ‡Fisher's Exact Test, §Kaplan- Meier test **Eastern Cooperative Oncology Group Performance Status

immunotherapy was applied to nine (11.5%) patients, and lung surgery was applied to five (6.4%) patients. Of the patients who developed relapse, 2.5% (two patients) could not receive treatment.

Fifty-nine (56.7%) patients died. The median OS was 21 months (11.2-30.8) in those with tumor cavitation, and 23 months (13.4-32.6) in those without (p=0.256). In univariate cox-regression analysis, factors that negatively affected OS were ≥65 age, ECOG performance status ≥2, presence of comorbidities, advanced stage, smoking ≥50 pack/year, chemoradiotherapy implementation, high SUVmax at diagnosis, high NLR, PLR, MLR, SII, HALP, LDH levels and presence of anemia (Table 2). In multivariate analysis, high NLR level and advanced stage were found to decrease OS (p=0.048, p=0.009).

When the OS is examined according to the stages, the survival decreased numerically in all stages in those with tumor cavitation (Stage I-II 64 vs 60.8 months p=0.937, Stage III-IV 27.7 vs 17.2 months p=0.017). However, the presence of tumor cavitation was found to significantly decrease OS in Stage III patients (40.53 vs 17.83 months, p=0.016, Figure 1).

When the Stage III patients were examined, it was seen that 60% (6/10) of the patients with tumor cavitation and 77.3% (17/22) of the patients without tumor cavitation had definitive chemoradiotherapy.

The presence of Stage III disease decreased OS in the presence of tumor cavitation (p=0.032).

Discussion

In our study, tumor cavitation was seen with a rate of 16.8% in lung SCCs. Most of the patients with tumor cavitation were men, patients with large tumor diameter, smokers, and advanced stage patients with comorbidities. Presence of tumor cavitation significantly reduced survival in Stage III patients. High NLR level and advanced stage reduced OS in lung SCCs.

Cavitations are abnormal spaces filled with air or fluid in the lung parenchyma. Infections, rheumatological diseases, septic embolism and malignancies play a role in its etiology. In addition, tumor cavitation may develop in oncological treatments. Studies have shown that the risk of tumor cavitation increases in advanced age, male gender, high smoking and advanced stages [13,14]. In our study, the majority of patients with tumor cavitation were male and in advanced stages. The frequency of tumor cavitation in lung SCC patients was similar to the literature. However, there was no statistically significant difference between smoking and the presence of cavitation due to the presence of heavy smoking in the etiology of lung SCCs.

There are conflicting results between the presence of tumor cavitation and prognosis in the literature [6,13,14]. Koladziesjshi et al. and Onn et al. showed that the presence of tumor cavitation negatively affects survival. Also, Singh et al. found that advanced age and tumor cavitation reduced OS in most advanced stage NSCLC patients [6,14,15]. However, there are also studies showing that the presence of tumor

Table 2. Factors affecting overall survival in univariate cox-regression analysis

		p	OR	95.0% CI	
		Univariate Cox Regression Analysis			
Age (Ref:<65 years)	≥65years	<0.001	3.287	1.907	5.668
Tumor Cavitation (Ref: None)	Present	0.265	1.345	0.799	2.263
Gender (Ref:Female)	Male	0.265	1.345	0.799	2.263
ECOG PS* (Ref:0-1)	ECOG PS 2	0.012	3.682	1.324	10.240
Comorbidities (Ref:None)	Available	0.001	2.591	1.507	4.454
Tumor size, cm (Ref: <7 cm)	≥7cm	0.484	1.256	0.663	2.382
Stage (Ref:Stage 1-2)	Stage 3 Stage 4	0.001	2.577	1.510	4.397
Smoking history (Ref:<50 pocket/year)	≥50pocket/year	0.001	26.137	3.595	190.050
Treatment (Ref:CRT†)	Others	<0.001	4.656	2.392	9.063
Lung Localisation (Ref: Peripheral)	Central	0.154	1.601	0.839	3.054
Treatment before SUVmax value		0.346	1.283	0.764	2.154
NLR‡ value (≥2.19 vs <2.19)		<0.001	1.111	1.065	1.159
PLR§ value (≥130.56 vs <130.56)		<0.001	3.888	2.225	6.794
MLR** value (≥0.41 vs <0.41)		<0.001	4.205	2.364	7.480
SII††value (≥604.65 vs <604.65)		<0.001	5.723	3.059	10.707
HALP‡‡ score (<29.15 vs ≥29.15)		<0.001	7.124	3.573	14.206
LDH§§ value		<0.001	4.490	2.463	8.186
Presence of anemia		0.009	1.001	1.000	1.002
Recurrence and/or metastasis		0.521	0.819	0.445	1.506
		Multivariate Cox Regression Analyses			
NLR‡ value (≥2.19 vs <2.19)		0.048	2.219	1.009	4.882
Stage (Ref:Stage 1-2)	Stage 3-4	0.009	15.476	1.980	120.963

*Eastern Cooperative Oncology Group Performance Status †Chemoradiotherapy ‡Neutrophil-Lymphocyte Ratio, §Platelet-Lymphocyte Ratio, **Monocyte-Lymphocyte Ratio, ††Systemic Inflamatuar Index ‡‡Hemoglobin albumin lymphocyte and platelet score §§Lactate Dehydrogenase

cavitation does not affect survival, as in the study of Coffey et al. also reported that tumor cavitation did not affect PFS and OS [4,13,16]. In our study, the presence of tumor cavitation significantly reduced survival in Stage-III patients, most of whom underwent chemoradiotherapy (40.53 vs 17.83 months p=0.016). Topkan et al. found that the presence of tumor cavitation reduced survival in Stage III patients who underwent chemoradiotherapy [17]. In the Phernambucq et al. studies, median OS was decreased in patients with tumor cavitation who received concomitant chemoradiotherapy, but it could not reach statistical significance (9.9 vs 16.3 months, p=0.09) [4]. Considering that definitive chemoradiotherapy is the main treatment in unresectable Stage III patients, it can be hypothesized that chemoradiotherapy may be a poor prognostic in the presence of tumor cavitation.

FDG-PET CT can detect necrosis in the tumor by measuring tissue metabolic activity. Studies have shown that OS decreases when tumor diameter and SUVmax increase in lung cancers [18]. However, Coffey et al. found in their study that the presence of tumor cavitation did not increase SUVmax [16]. In our study, high SUVmax level decreased OS in univariate analysis, but it did not reach significance in multivariate analysis (p<0.001, p=0.058). This situation can be explained by the fact that the cavitary lesions are usually large in volume, and the high SUVmax level measured in living cells due to central tumor necrosis is low due to the large volume.

Tumor cavitation is a marker of necrosis because the risk of infection is increased in patients with tumor cavitation [13]. NLR, PLR, MLR, SII and HALP scores are indexes that reflect the immune response in lung cancer and have prognostic significance [8-12]. In the study of Wang et al. in early stage lung cancer patients, MLR was reported as an independent factor affecting survival [9]. Aduquaye et al. found that high NLR was associated with recurrence-free survival among inflammatory markers in early-stage lung cancer [19]. In a recent study conducted by Winther-Larsen et al. on 5320 stage I-IV non-small cell lung cancer patients, high NLR, PLR and MLR were found to be associated with decreased OS [20]. This is the first study in the literature to show the relationship between cavitary lesions and inflammatory indexes. Contrary to expectations in our study, MLR and LHD levels were found to be lower in patients with tumor cavitation at the time of diagnosis. Although it is known that high LDH concentration has a poor prognostic role in lung cancer, LDH level is affected by many factors [21]. In addition, serum inflammatory markers are thought to be affected by environmental and hereditary factors [22]. However, in our study, high NLR level was found to be associated with reduced OS, as is frequently shown in the literature.

Limitations: The limitations of our study are its retrospective nature and the limited number of patients. Another limitation of our study is the inability to evaluate the formation mechanisms of cavitary lesions or the level of response to treatment.

Conclusion

The presence of tumor cavitation is especially important for lung SCCs. Due to delayed diagnosis and complications, these tumors usually reach large diameters and are caught in advanced stages. In our study, it was shown that tumor cavitation negatively affects the prognosis especially in stage III lung SCCs.

Among the inflammatory indices, high NLR has been shown to decrease survival in lung SCCs. No increase in inflammatory indices was detected in patients with tumor cavitation. This may be due to the inclusion of patients at different stages in the study and other factors affecting inflammatory indices. More comprehensive studies are needed on this subject.

Tumor cavitation differs with its mechanism, biology and clinical course. Care should be taken in the follow-up and treatment planning of these patients, and they should be closely monitored for complications.

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Scientific Responsibility Statement
The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement
All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest
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